# General

## Guideline Title

Guidelines for the diagnosis and treatment of cobalamin and folate disorders.

## Bibliographic Source(s)

## Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Guidelines on the investigation and diagnosis of cobalamin and folate deficiencies. A publication of the British Committee for Standards in Haematology. BCSH General Haematology Test Force. Clin Lab Haematol. 1994 Jun;16(2):101-15.

# Recommendations

## Major Recommendations

Definitions for the quality of the evidence (A–C) and strength of recommendations (strong [Grade 1], weak [Grade 2]) are given at the end of the "Major Recommendations" field.

Cobalamin Deficiency

Tests to Confirm/Diagnose Cobalamin Deficiency

1. A blood film showing oval macrocytes and hypersegmented neutrophils in the presence of an elevated mean cell volume (MCV) may alert the clinician to the presence of underlying cobalamin or folate deficiency (Grade 2B).
2. Cobalamin and folate assays should be assessed concurrently due to the close relationship in metabolism (Grade 1A).
3. The writing group recommends adoption of reporting for cobalamin assay results in pmol/l (Grade 2C).
4. A serum cobalamin cut-off level of either 148 pmol/l (200 ng/l) or one derived from a local reference range should be used as evidence of cobalamin deficiency in the presence of a strong clinical suspicion (Grade 2B).
5. The report providing the result of a serum cobalamin assay should include the following:
    a. The interpretation of the result should be considered in relation to the clinical circumstances.
    b. Falsely low serum cobalamin levels may be seen in the presence of folate deficiency or technical issues.
    c. Neurological symptoms due to cobalamin deficiency may occur in the presence of a normal MCV (Grade 1B).
6. Plasma total homocysteine (tHcy) and/or plasma methylmalonic acid (MMA), depending on availability, may be considered as supplementary tests to determine biochemical cobalamin deficiency in the presence of clinical suspicion of deficiency but an indeterminate

serum cobalamin level (Grade 2B).

    a. Although plasma tHcy is a sensitive marker of cobalamin deficiency, plasma MMA is more specific.

    b. Both assays have to be interpreted in relation to renal function.

7. Holotranscobalamin (HoloTC) is suggested as a suitable assay for assessment of cobalamin status in a routine diagnostic laboratory in the future (Grade 1B).

## Tests to Determine the Aetiology of Cobalamin Deficiency

1. All patients with anaemia, neuropathy or glossitis, and suspected of having pernicious anaemia, should be tested for anti-intrinsic factor antibody (IFAB) regardless of cobalamin levels (Grade 1A).

2. Patients found to have a low serum cobalamin level in the absence of anaemia, and who do not have food malabsorption or other causes of deficiency, should be tested for IFAB to clarify whether they have an early/latent presentation of pernicious anaemia (Grade 2A).

3. Anti-gastric parietal cell (GPC) antibody testing for diagnosing pernicious anaemia is not recommended (Grade 1A).

## Treatment of Cobalamin Deficiency

1. Treatment of established cobalamin deficiency should follow the schedules in the British National Formulary (BNF) (Grade 1A).

2. Initial treatment with oral cobalamin may not be appropriate in pernicious anaemia, but may be considered in maintenance or correction of suboptimal levels in asymptomatic patients (Grade 2C).

## Clinical Approach to Investigation and Treatment of Cobalamin Associated Disorders

*Low Serum Cobalamin and Anaemia or Strong Objective Clinical Features of Glossitis or Peripheral Neuropathy* (See Algorithm 1 in the original guideline document.)

1. Patients suspected of having pernicious anaemia should be tested for IFAB. Patients found to be positive should have lifelong therapy with cobalamin (Grade 1A).

2. Patients negative for IFAB, with no other causes of deficiency, may still have pernicious anaemia and should be treated as anti-IFAB-negative pernicious anaemia. Lifelong therapy should be continued in the presence of an objective clinical response. (Grade 2A).

*Borderline or Normal Serum Cobalamin, in the Presence of Anaemia or Other Symptoms (False Normal Cobalamin Levels)*

1. Serum cobalamin level of greater than 148 pmol/l (200 ng/l) in the presence of a strong clinical suspicion of cobalamin deficiency should be evaluated further with MMA, tHcy or HoloTC and a trial of hydroxocobalamin given to ascertain any clinical improvement (Grade 1C).

*Low Serum Cobalamin without Anaemia or Other Significant Objective Parameters (Low Cobalamin of Uncertain Significance)* (See Algorithm 2 in the original guideline document.)

1. In patients with serum cobalamin levels of 'subclinical deficiency' on two occasions, an empirical trial of treatment with oral cyanocobalamin (50 μg daily for 4 weeks) should be given. Strict instructions should be given to patients to seek immediate medical attention if symptoms of neuropathy develop. The cobalamin level should be rechecked after 3 months, and second line tests considered if there is no improvement (Grade 2C).

*Low Serum Cobalamin on Metformin*

1. No definitive advice can be given on the desirable frequency of monitoring of serum cobalamin in patients with type II diabetes mellitus on metformin therapy, but it is recommended that serum cobalamin is checked in the presence of strong clinical suspicion of deficiency (Grade 2B).

2. If serum cobalamin levels are reduced, patients should have tests for anti-IFAB because the concurrence of pernicious anaemia with diabetes should be considered. If positive, the patient should have lifelong treatment with replacement cobalamin. If negative, the reduced level may be purely as a result of metformin, although underlying antibody negative pernicious anaemia (AbNegPA) cannot be excluded. Treatment with oral cobalamin may be considered (50 μg for 1 month); subsequent monitoring of serum cobalamin after 6 months and then at yearly intervals is suggested (Grade 2C).

3. Currently no recommendations can be given on prophylactic administration with oral cobalamin in patients taking metformin.

*Patients on Hormone Replacement Therapy (HRT) and Oral Contraception*

1. Asymptomatic women taking oral contraception or HRT with mildly reduced serum cobalamin (110pmol/l to 148 pmol/l; 150ng/l to 200 ng/l) do not require further investigation but should be advised to review their dietary intake of cobalamin rich foods, and cobalamin

supplements may be considered (Grade 1B).

*Pregnancy*

1. Serum cobalamin levels fall during pregnancy and are less reliable in determining underlying deficiency (Grade 1A).
2. During pregnancy, in the presence of strong suspicion of underlying deficiency, a short course of empirical hydroxocobalamin should be given, with further investigations post-partum (Grade 2C).
3. HoloTC may be more reliable than serum cobalamin in determining deficiency in pregnancy, and is recommended as the test of choice, if available (Grade 1B).

*Vegetarians*

1. Vegetarians, particularly strict vegans, should be considered for monitoring of their cobalamin level according to clinical assessment (Grade 2C).
2. Dietary alterations or oral supplementation may be considered according to the clinical situation (Grade 2C), particularly during pregnancy and breast-feeding.

*Poor Absorption Due to Gastrointestinal Surgery or Disease*

1. Patients who have had bariatric surgery should have their cobalamin status monitored and are likely to need cobalamin supplementation via a route depending upon the type of surgery (Grade 1B).
2. Patients with food-bound cobalamin malabsorption may benefit from low dose oral replacement (Grade 2C).

*Infancy*

1. Reduced serum cobalamin levels in infancy in the presence of clinical features should be treated promptly to prevent long term neurological sequelae (Grade 1A).
2. In the presence of clinical suspicion of underlying cobalamin deficiency, even in the presence of normal serum cobalamin levels, further biochemical tests including MMA and tHcy are recommended (Grade 1B). The role of HoloTC in this context is undefined. Further investigation to define any possible genetic abnormalities should be referred to a specialist centre. No specific recommendation can be made regarding treatment since each case has to be judged individually.
3. No specific recommendations can currently be made in relation to breastfeeding associated biochemical low cobalamin status in asymptomatic infants.

Folate Deficiency

Tests to Diagnose Folate Deficiency

1. A serum folate level <7 nmol/l (3 µg/l) is indicative of folate deficiency (Grade 1B).
2. Routine red cell folate testing is not necessary since serum folate alone is sufficient in most cases (Grade 1A).
3. In the presence of strong clinical suspicion of folate deficiency, despite a normal serum level, a red cell folate may be undertaken, having ruled out cobalamin deficiency (Grade 2B).
4. Plasma tHcy can be measured to confirm suspected folate deficiency only in special circumstances; a level above 15 µmol/l could be indicative of folate deficiency but must be assessed in relation to local reference ranges (Grade 2B).

Clinical Approach to Investigation and Treatment of Folate Associated Disorders

1. Folate status is generally checked in clinical situations similar to those of cobalamin deficiency (Grade 1A).
2. Consultation of the BNF and Summary of Product Characteristics is recommended for clarifying any suspicion of low serum folate levels associated with prescribed medications.

Treatment of Folate Deficiency

1. Treatment of folate disorders should follow the schedules in the BNF (Grade 1A).

Definitions:

Quality of Evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge

and whether further research could change what we known or is certain.

(A) High: Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

(B) Moderate: Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g., inconsistent results, imprecision - wide confidence intervals or methodological flaws - e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low: Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.

Strength of Recommendations

Strong (Grade 1): Strong recommendations (Grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (Grade 2): Where the magnitude of benefit or not is less certain a weaker Grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

## Clinical Algorithm(s)

The following algorithms are provided in the original guideline document:

- Algorithm 1: Investigation and management of patients presenting with a strong clinical suspicion of cobalamin deficiency and objective parameters to support this
- Algorithm 2: Investigation of low serum cobalamin in patients without objective clinical parameters

# Scope

## Disease/Condition(s)

Cobalamin and folate disorders

## Guideline Category

Diagnosis

Evaluation

Management

Treatment

## Clinical Specialty

Family Practice

Hematology

Internal Medicine

Obstetrics and Gynecology

Pediatrics

# Intended Users

Advanced Practice Nurses

Clinical Laboratory Personnel

Nurses

Physician Assistants

Physicians

# Guideline Objective(s)

To provide an evidence-based approach to the diagnosis and management of cobalamin and folate disorders

# Target Population

All patients with or suspected of having serum cobalamin and folate disorders

# Interventions and Practices Considered

Evaluation/Diagnosis

1. Blood film in the presence of an elevated mean cell volume (MCV)
2. Serum cobalamin assay (reported in pmol/l) and folate assay assessed concurrently
3. Plasma total homocysteine (tHcy)
4. Plasma methylmalonic acid (MMA)
5. Holotranscobalamin (HoloTC)
6. Anti-intrinsic factor antibody (anti-IFAB) testing
7. Serum folate testing
8. Red cell folate testing only if indicated (not routinely recommended)
9. Anti-gastric parietal cell (anti-GPC) antibody testing (not recommended)

Treatment/Management

1. Oral cobalamin therapy (oral cyanocobalamin)
2. Trial of hydroxocobalamin (if indicated)
3. Dietary alterations
4. Folic acid
5. Management of specific patient populations
   - Patients with type II diabetes mellitus on metformin
   - Patients on hormone replacement therapy (HRT) and oral contraception
   - Pregnant women and infants
   - Vegetarians
   - Patients with poor absorption due to gastrointestinal surgery or disease

# Major Outcomes Considered

- Megaloblastic anaemia
- Neurological disability
- Cardiovascular health consequences

# Methodology

## Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

## Description of Methods Used to Collect/Select the Evidence

The Guidelines Writing Group (GWG) reviewed publications up to 2013 identified via the PubMed and Cochrane databases using index terms including cobalamin, vitamin B12, folate, methylmalonic acid (MMA), homocysteine, holotranscobalamin, and combined with deficiency, treatment, pregnancy, oral contraceptive, metformin, bariatric surgery and infancy.

## Number of Source Documents

Not stated

## Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

## Rating Scheme for the Strength of the Evidence

Quality of Evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what we known or is certain.

(A) High: Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

(B) Moderate: Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g., inconsistent results, imprecision - wide confidence intervals or methodological flaws - e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low: Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.

## Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review

## Description of the Methods Used to Analyze the Evidence

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was used to assess the grades of evidence (see the "Rating Scheme for the Strength of the Evidence" field).

## Methods Used to Formulate the Recommendations

Expert Consensus

## Description of Methods Used to Formulate the Recommendations

The previous British Society for Haematology guidelines on investigation and diagnosis of cobalamin and folate deficiencies (British Committee for Standards in Haematology 1994) were published 20 years ago and this update reflects changes in diagnostic and clinical practice.

These guidelines aim to provide an evidence-based approach to diagnosis and management of cobalamin and folate disorders. However, such evidence, particularly in the form of randomised controlled trials, is lacking. As a result, these guidelines provide a pragmatic approach to the testing and treatment of cobalamin and folate disorders, with recommendations based, as far as possible, on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system. In the majority of situations, the recommendations inevitably rely more on clinical judgement and consensus than objective laboratory data.

## Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Strong (Grade 1): Strong recommendations (Grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (Grade 2): Where the magnitude of benefit or not is less certain a weaker Grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

## Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

## Method of Guideline Validation

External Peer Review

Internal Peer Review

## Description of Method of Guideline Validation

Initial review of the manuscript was performed by members of the General Haematology Task Force of the British Committee for Standards in Haematology (BCSH), the executive committee, and a sounding board drawn from United Kingdom (UK) haematologists.

# Evidence Supporting the Recommendations

## Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for selected recommendation (see the "Major Recommendations" field).

# Benefits/Harms of Implementing the Guideline Recommendations

## Potential Benefits

## Potential Harms

- Hydroxocobalamin side effects include itching, exanthema, chills, fever, hot flushes, nausea, dizziness and exceptionally, anaphylaxis. This may be due to hypersensitivity to cobalt or any of the other components of the medication. Acneiform eruptions have been reported rarely. Due to cross-sensitivity of hydroxocobalamin and cyanocobalamin, treatment of patients may be a challenge. Skin patch testing may help to choose an appropriate product. If absolutely necessary, treatment may be considered under hydrocortisone cover in a hospital setting where severe hypersensitivity can be managed.
- Care must be taken if low dose oral cyanocobalamin supplements are prescribed, as such an approach risks the suboptimal treatment of latent and emerging pernicious anaemia with possible inadequate treatment of neurological features.
- There is no clear consensus on the level of serum folate that indicates deficiency. Conventionally, clinicians have used serum folate lower than 7 nmol/l (3 μg/l) as a guideline since the risk of megaloblastic anaemia greatly increases below this level. However, there is a sizeable 'indeterminate zone' (between approximately 7 and 10 nmol/l [3 and 4.5 μg/l]). Therefore a low serum folate should be taken as suggestive of deficiency rather than as a highly sensitive diagnostic test.
- Some serum cobalamin assays may give false normal results in sera with high titre anti-intrinsic factor antibodies.

# Qualifying Statements

## Qualifying Statements

While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the British Society for Haematology nor the publishers accept any legal responsibility for the content of these guidelines.

# Implementation of the Guideline

## Description of Implementation Strategy

An implementation strategy was not provided.

## Implementation Tools

Audit Criteria/Indicators

Clinical Algorithm

> For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

# Institute of Medicine (IOM) National Healthcare Quality Report Categories

## IOM Care Need

Getting Better

Living with Illness

## IOM Domain

Effectiveness

# Identifying Information and Availability

## Bibliographic Source(s)

Devalia V, Hamilton MS, Molloy AM, the British Committee for Standards in Haematology. Guidelines for the diagnosis and treatment of cobalamin and folate disorders. Br J Haematol. 2014 Aug;166(4):496-513. [147 references] PubMed

## Adaptation

Not applicable: The guideline was not adapted from another source.

## Date Released

1994 Jun (revised 2014 Aug)

## Guideline Developer(s)

British Committee for Standards in Haematology - Professional Association

## Source(s) of Funding

British Society for Haematology (BCSH)

## Guideline Committee

Guidelines Writing Group (GWG)

## Composition of Group That Authored the Guideline

*Writing Group Members*: Vinod Devalia, Princess of Wales Hospital, Bridgend; Malcolm S Hamilton, Royal Devon and Exeter Hospital, Exeter; Anne M Molloy, School of Medicine, Trinity College Dublin, Ireland

## Financial Disclosures/Conflicts of Interest

Conflict of Interest

AM has received funding from Axis Shield Diagnostics to study the clinical utility of holotranscobalamin.

## Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Guidelines on the investigation and diagnosis of cobalamin and folate deficiencies. A publication of the British Committee for Standards in Haematology. BCSH General Haematology Test Force. Clin Lab Haematol. 1994 Jun;16(2):101-15.

## Guideline Availability

Electronic copies: Available from the British Journal of Haematology Web site _____.

Print copies: Available from the British Committee for Standards in Haematology; Email: bcsh@b-s-h.org.uk.

## Availability of Companion Documents

Recommendations for audit are available in the original guideline document _____.

## Patient Resources

None available

## NGC Status

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## Copyright Statement

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